

Section 4

Toxicity Assessment

PCBs have been associated with both cancer and noncancer health effects. Noncancer health effects include neurotoxicity, reproductive and developmental toxicity, immune system suppression, liver damage, skin irritation, and endocrine disruption (EPA 1996). A toxicity profile summarizing carcinogenic and noncarcinogenic health effects associated with PCBs is included in Appendix E. A brief overview of key studies of human health effects of PCBs is presented below.

4.1 Summary of Health Effects Associated with PCBs

ATSDR and EPA have jointly developed a technical paper, Public Health Implications of Polychlorinated Biphenyls (PCBs) Exposure. Human health studies discussed in this paper indicate that exposure to PCBs have been linked to the following health impacts:

- Effects on reproductive function in women
- Neurobehavioral and development deficits in newborns and school-age children from in utero exposure
- Liver disease, immune function impacts, and thyroid effects
- Increased cancer risks

Several studies have demonstrated a correlation between fish consumption by mothers, and developmental disorders and cognitive deficits in children. In the first of these studies, conducted by Jacobson (Jacobson, et al. 1985, 1990a, 1990b), statistically significant decreases in gestational age, birth weight, and head circumference were observed and continued to be evident 5 to 7 months after birth. Neurobehavioral deficits were observed including depressed responsiveness, impaired visual recognition, and poor short-term memory at 7 months of age, which continued to be present at 4 years of age. While recognized limitations exist in these studies, including the pooling of blood samples, which is no longer a recognized technique, more recent studies have provided supportive evidence of the relationship between PCB exposure and developmental effects.

In a study of prenatal exposure and neonatal behavioral assessment scale (NBAS) performance, cord blood PCBs, DDE, HCB, Mirex, lead, and hair mercury levels were determined for 152 women who reported never consuming Lake Ontario fish and 141 women who reported consuming at least 40 PCB-equivalent pounds of Lake Ontario fish over a lifetime. Past PCB exposure was related to impaired performance on those NBAS clusters associated with fish consumption, namely habituation and autonomic clusters. Results revealed significant linear relationships between the most heavily chlorinated PCBs and performance impairments 25 to 48 hours after birth. Higher prenatal PCB exposure was also associated with nonspecific performance

impairment (Stewart, et al. 2000). Exposure to lower molecular weight PCBs (i.e., PCBs containing fewer chlorine atoms) was unrelated to NBAS performance.

Studies in Japan and Taiwan of PCB exposure from consumption of contaminated rice oil have contributed to evidence of an association between PCBs and neurobehavioral effects. The illnesses were originally referred to as Yusho disease in Japan and Yu-Cheng disease in Taiwan. In earlier studies (Bandiera, et al. 1984; Kunita, et al. 1984; Masuda and Yoshimura 1984; Ryan, et al. 1990; ATSDR 1996) co-contaminants in the rice oil, particularly chlorinated dibenzofurans (CDFs), were considered to be the primary causal agent. Recent studies, however, involving a reexamination of previous studies and newer results from a study of children born later to exposed mothers have demonstrated developmental delays associated with maternal exposure to PCBs and CDFs (Guo, et al. 1995; Chao, et al. 1997).

A study of Inuit women from Hudson Bay indicated an association between levels of PCBs and dichlorodiphenylethene (DDE) in breast milk and a statistically significant reduction in male birth length (Dewailley, et al. 1993a). No significant differences were observed between male and female newborns for birth weight, head circumference, or thyroid-stimulating hormone.

A study of 338 infants of mothers occupationally exposed to PCBs during the manufacture of capacitors indicated a decrease in gestational age (6.6 days) and a reduction in birth weight (153 grams) at birth in infants of mothers directly exposed to PCBs (Taylor, et al. 1984). A follow-up study of 405 women in this population demonstrated that serum total PCB levels in women with direct exposure to PCBs were more than four-fold higher than for women in indirect-exposure jobs. A decrease in birth weight and gestational age was found for the infants of these women (Taylor, et al. 1989).

Immune system effects on persons exposed to PCBs have been reported in several studies. A significant negative correlation between weekly consumption of fish containing PCBs from the Baltic Sea and white cell count was reported (Svensson 1994). Immune system effects were reported in Inuit infants who were believed to have received elevated levels of PCBs and dioxins from their mother's breast milk. Effects included a decline in the ratio of the CD4+ (helper) to CD8+ (cytotoxic) T-cells at ages 6 and 12 months (Dewailley, et al. 1993). Infants examined from birth to 18 months who were exposed to PCBs/dioxins in the Netherlands exhibited lower monocyte and granulocyte counts and increases in the total number of T-cells and the number of cytotoxic T-cells (Weisglas-Kuperous, et al. 1995). An increase in serum PCB levels was associated with a decrease in natural killer cells (Hagamar, et al. 1995).

Effects on the thyroid have been reported in a study of the Dutch population. Higher CDD, CDF, and PCB levels in human milk correlated significantly with lower plasma levels of maternal total triiodothyronine and total thyroxine and higher plasma levels

of thyroid-stimulating hormone in infants during the second and third month after birth (ATSDR 1998).

Occupational studies show some increases in cancer mortality in workers exposed to PCBs. Significant excesses of cancer mortality were found for liver, gall bladder, and biliary tract cancer (Brown 1987), however, co-exposure to other chemicals in the workplace limits the strength of the association to PCBs. Mortality from gastrointestinal tract cancer in males and hematologic neoplasms in females was reported for capacitor workers in Italy (Bertazzi, et al. 1987). Limitations in this study include a small number of cases, short exposure period, and lack of pattern or trend when data were analyzed by duration of exposure. The results of these studies have been evaluated and are considered inconclusive by ATSDR (1996).

Evidence of an association between exposure to PCBs by capacitor workers and mortality from malignant melanoma was reported (Sinks, et al. 1992). The workers were also exposed to various solvents. More deaths were observed than expected for malignant melanoma (8 observed versus 2 expected) and cancer of the brain and central nervous system (5 observed versus 2.8 expected). Limitations include a small number of cases, insufficient monitoring data, unknown contribution of exposure to solvents, and possible bias due to the healthy worker effect. The results of this study have been evaluated and are considered inconclusive by ATSDR.

A recent study of male and female capacitor workers reported mortality from all cancers was significantly below expected for hourly male workers and comparable to expected for female workers (Kimbrough, et al. 1999). Limitations with this study include:

- Exposed and unexposed workers were included as one group diluting any potential cancer findings
- Seventy-six percent of the workers never had exposure to PCBs
- Only 4 percent of the workers had any PCB blood data and only 2 percent worked in jobs with high exposure to PCBs
- Seventy-nine percent of the workers who did die of cancer had PCB exposures less than 1 year

The ATSDR has stated it is untenable to dismiss concerns for carcinogenicity of PCBs. In 1999, the ATSDR convened an Expert Panel Review of the Toxicological Profile for PCBs. The panel concurred that the Kimbrough study of General Electric capacitor workers could not be used to dismiss the carcinogenic potential of PCBs (Bove, et al. 1999).

For reasons such as those above, EPA also concludes that the limitations of the Kimbrough study prevent conclusions to be drawn regarding the carcinogenicity of

PCBs. While all human studies have limitations and confounders, controlled animal studies, such as a long-term bioassay conducted by General Electric (Mayes 1998) provide conclusive evidence that PCBs, including the lower chlorinated forms (i.e., Aroclor 1016 and 1242) cause cancer in experimental animals. For this reason, the International Agency for Research on Cancer and EPA have concluded that the PCBs are probable human carcinogens. These conclusions are independently consistent with the National Toxicology Program's eighth Report on Carcinogens, which lists PCBs as "reasonably anticipated to be human carcinogens."

A recent study demonstrated a strong dose-response relationship between total lipid-corrected serum PCB concentrations and the risk of non-Hodgkin lymphoma (Rothman, et al. 1997). These findings are consistent with another study where residues of PCBs in adipose tissue of non-Hodgkin's lymphoma patients were higher than those of control patients (Hardell, et al. 1996). In studies of capacitor workers, significantly increased risks were reported for lymphatic/hematological malignant (LHM) diseases among female capacitor workers but non-significant increases were found for male workers (Bertazzi, et al. 1987). Two other studies found no evidence of increase in LHM among workers (Brown 1987; Sinks, et al. 1992).

Health Studies in the Great Lakes Basin

Research indicates that the primary pathway of exposure to PCBs in the Great Lakes region is from fish consumption. Recent evidence indicates an association between PCB exposures through fish consumption and reproductive and developmental effects. Newborns of mothers in the high fish consumption category exhibited a greater number of abnormal reflexes, less mature autonomic responses, and less attention to visual and auditory stimuli (Lonky, et al. 1996).

The Lake Michigan Maternal Infant Cohort study was the first epidemiologic investigation to demonstrate an association between the self-reported amounts of Lake Michigan fish eaten by pregnant women and behavioral deficits in their newborns. The 242 infants born to mothers who had eaten the greatest amount of contaminated fish during pregnancy had (1) more abnormally weak reflexes; (2) greater motor immaturity and more startle responses; and (3) less responsiveness to stimulation (ATSDR 1998). A follow-up examination of 212 children indicated that the neurodevelopmental deficits found during infancy and early childhood still persisted at age 11 years (Jacobsen and Jacobsen 1996).

In a study of nervous system dysfunction in adults exposed to PCBs and other persistent toxic substances, motor slowing and attention difficulties were directly related to the frequency of consumption of St. Lawrence Lakes fish (Mergler 1997, 1998).

In an ongoing study of Native Americans in Minnesota, Wisconsin, and Michigan preliminary results indicated elevated serum PCB levels were correlated with self-reported diabetes and liver disease (Dellinger, et al. 1997; Tarvis, et al. 1997;

Gerstenberger, et al. 1997). The average annual fish consumption rate was 23 grams per day.

In a study of the PCB congener profile in the serum of humans consuming Great Lakes fish, an established cohort of persons with robust exposure to contaminants in recreationally caught Great Lakes fish were shown to have significant quantities of serum PCBs still present 15 years after enrollment in the study. The current levels of PCBs in this group were far above those found in enrollees of more recent fish eater studies. Identification of the PCB profile in fisheaters and non-fish eaters revealed the presence of several congeners that have the potential to affect biologic or health outcomes. Investigators are currently in the process of evaluating neuropsychologic function and thyroid function in the Lake Michigan fisheaters for which PCB congener profiles were established (Humphrey, et al. 2000)

The Kalamazoo River Angler Survey (MDCH 2000b) included a second phase, which included a health survey and biological testing. In this second phase, individual self-reported medical information and fish consumption patterns were obtained and chemical analyses for PCBs, DDE, and mercury was performed on blood samples of 151 out of the original 938 survey participants. The study attempted to analyze for possible associations between chemical residue levels and self-reported health problems for fisheaters and compared chemical residue data from this study cohort to other fish eating populations previously studied.

The study reported that "medical problems reported as subjective symptoms (upset stomach, nausea, headache, or dizziness) were not measurable or quantifiable in an objective way. Statistically significant associations were not found between contaminant residues levels and self-reported medical problems. However, those anglers who considered themselves to be in good health appeared to be less likely to have blood PCB levels above median values for the aggregate group than anglers who considered themselves to be in fair/poor health."

Significantly higher levels of PCBs were found in fisheaters compared with non-fish eaters. The geometric mean for fisheaters was 2.1 ppb PCBs in blood and for non-fish eaters was 1.11 ppb PCBs in blood. Increasing residue levels for PCBs suggested a good correlation with age reflecting the persistence of these compounds in human tissues and possible higher past exposures. In contrast to previous studies of sport anglers, the Kalamazoo River Survey appears to indicate lower exposure to PCBs. Lake Michigan open water fisheaters were first evaluated in 1979-1980 and reevaluated in 1989 (Humphrey 1988; Hovinga, et al. 1992). The Lake Michigan fisheaters consumed an annual average of 32 pounds (64 meals per year) of sport-caught fish, whereas the Kalamazoo anglers consumed an annual average of 9 pounds (18 meals per year) of sport-caught fish. The Kalamazoo fisheaters more closely resembled the non-fish eaters in the Lake Michigan study.

In a comparison of Kalamazoo anglers with a survey of anglers on Wisconsin inland lakes and rivers (Fiore 1989), the following was observed: (1) Kalamazoo anglers ate on average less fish than the Wisconsin anglers but had higher PCB levels; (2) 59 of the Wisconsin anglers had no detectable PCBs while only 10 Kalamazoo River anglers were non-detectable; (3) the upper range of serum PCBs (73 ppb) reported in Kalamazoo was more than two and one-half times the upper range seen in Wisconsin (27.1 ppb).

Limitations of Phase II of the Kalamazoo River Angler Survey include: (1) selection bias in that the study group was self-selected; (2) fish consumption within the past 12 months was used as the exposure variable, rather than historic consumption; (3) response bias due to participants knowing the purpose of the study; and (4) biases associated with self-reporting health effects.

4.2 Cancer Dose Response Evaluation

A recent reevaluation of the cancer dose response relationship for PCBs introduced a new approach for evaluating cancer risks associated with PCB exposure. This approach includes a range of cancer slope factors to be used depending on the medium of exposure and the form of the PCBs (persistent PCBs, dioxin-like congeners, and tumor-promoting congeners). Other features of this approach include:

- Upper-bound and central slope estimates, with guidance on when each is appropriate
- A procedure for adjusting exposure duration to include internal exposure, reflecting persistence in the body
- Incorporation of biologically-based modeling results of tumor-promotion and cell dynamics
- Application of new principles from EPA's cancer guideline revisions (EPA 1994a, 1994b)

Three tiers of human slope factors for environmental PCBs have been developed by EPA as presented in Table 4-1. Exposure pathways to be evaluated in the HHRA fall in the high risk and persistence category with the exception of inhalation of volatile PCBs, which is in the low risk and persistence category. The upper bound slope factor (2 mg/kg-d^{-1}) is used to quantify risks for all pathways except for inhalation.

Table 4-1 Range of PCB Slope Factors, API\PC\KR Site

Level of Risk/ Resistance	Slope Factors (mg/kg-day) ⁻¹		Criteria for Use
High Risk and Persistence	2.0	1.0	Food chain experiences Sediment or soil ingestion Dust or aerosol inhalation Dermal exposure (if absorption factor) Dioxin-like, tumor-promoting, or persistent congeners Early life exposures
Low Risk	0.4	0.3	Water ingestion Inhalation of Volatile PCBs Dermal exposure (if no absorption factor)
Lowest Risk and Persistence	0.07	0.04	Congeners with more than 4 chlorines comprise less than 0.5 percent of total PCBs

4.3 Noncancer Dose Response Evaluation

EPA has developed reference doses (RfDs) for evaluation of noncancer health effects for two Aroclors - Aroclor 1016 and 1254. Reference concentrations (RfC) have not been developed for evaluation of inhalation exposures. RfDs are therefore used to evaluate ingestion, dermal, and inhalation exposures. The health endpoint for Aroclor 1016 is reproductive effects. The health endpoint for Aroclor 1254 is immunotoxicity (EPA 1999).

Aroclor 1248 is a prevalent contaminant at the site. EPA has not developed an RfD (or other toxicity values) for Aroclor 1248 because a serious health effect, or Frank Effect (death of an offspring), was observed at the lowest dose level received by Rhesus monkeys. In general, Rhesus monkeys have shown adverse effects to PCB mixtures at doses 10-fold lower than in other species. As stated in the *Integrated Risk Information System (IRIS)* file, EPA considers these data inadequate for the derivation of an oral RfD and the chemical is classified as "Non Verifiable." A secondary source of toxicity values, the *Health Effects Assessment Summary Tables* (EPA 1997) does not provide an RfD for Aroclor 1248.

In the absence of an RfD for Aroclor 1248, the RfD for Aroclor 1254 has been used to assess risks associated with exposure to Aroclor 1248. Studies conducted on both mixtures used Rhesus monkeys. The lowest dose administered in the Aroclor 1248 study was 0.03 mg/kg-day. The lowest dose administered in the Aroclor 1254 study was 0.005 mg/kg-day. Observed health effects at the lowest dose in the Aroclor 1254 study included impairment of various immunologic functions. These effects are considered appropriate to determine "lowest observed adverse effects levels" (LOAELS). The RfDs used to evaluate noncancer health effects are presented in Table 4-2.

Table 4-2 Noncancer Toxicity Date – Oral/Dermal/Inhalation, API/PC/KR Site

Chemical of Potential Concern	Chronic/ Subchronic	Oral RfD Value	Oral RfD Units	Primary Target Organ	Combined Uncertainty/ Modifying Factors	Sources of RfD: Target Organ	Dates of RfD: Target Organ ⁽¹⁾ (MM/DD/YY)
Aroclor 1254	Chronic	2.0E-05	mg/kg-day	Immune system - decreased antibody (IgG and IgM) response to sheep erythrocytes	300/1	IRIS	03/08/00
Aroclor 1016	Chronic	7.0E-05	mg/kg-day	Reproductive effects - reduced birth weights	100/1	IRIS	03/08/00

- (1) For IRIS values, provide the date IRIS was searched.
For Heast values, provide the date of HEAST
For NCEA values, provide the date of the article provided by NCEA.